### **REMARKS**

#### Formal Matters

A substitute specification, revised sequence listing and formal drawings are provided in order to correct various errors of form. Responsive to the Examiner's remark concerning the priority information, the paragraph at page 1, line 12 has been appropriately revised.

In amended Figures 1A-1E, Figures 2A-2B, Figures 3A-3D, Figure 4, Figure 5, Figures 6A-6F, Figure 7A-7B, Figures 8A-8D, Figure 9, Figure 10A-10D and Figure 11A-B, extraneous text was removed from the Figures.

Claims 29-54 remain in this application. No claim has been canceled. Claims 29, 39 and 49 are amended. No new matter is added by the amendments.

Support for the amendments to claims 29, 39, 49 is found at least at page 49, lines 33-36.

In view of the Examiner's earlier 6-way restriction requirement in parent application USSN 09/292,505, now U.S.P. 6,348,575, applicant retains the right to present previously withdrawn and cancelled claims in a divisional application.

#### The Rejection under 35 U.S.C. § 101

Claims 29-34, 37, 39-44, 47, 49-50 and 53 are rejected under 35 U.S.C. § 101 allegedly for being directed to non-statutory subject matter.

In response, Applicants amendment renders the rejection moot.

### The Rejection under 35 U.S.C. § 102(e)

Claims 29-35, 37-45, 47-51, and 53-54 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,309,879. Specifically, the Examiner has alleged that the above claims are drawn to antibodies which bind to polypeptides that are at least 91%, 92%, 93%, 95% or 100% identical to SEQ ID NO:2. The Examiner further alleges that the '879 patent not only teaches a polypeptide sequence that is 99.6% identical to SEQ ID NO:2, but also antibodies binding to such polypeptide sequence.

Response to Office Action mailed on: December 20, 2004

In response, Applicants respectfully submit that the 6,309,879 patent was the losing party to Applicants' related application USSN 09/060,939, having the same inventors and filing date as the parent application (USSN 09/292,505, U.S.P. 6,348,575) of the pending application. The U.S.P.T.O. has already determined in a prior action that Applicants are the actual inventors of the subject matter claimed in the '879 patent. A copy of the final decision from Interference 105,081 awarding all of claims 1-13 of '879 patent to Applicant's 09/060,939 application appears in the Appendix.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 29-35, 37-45, 47-51, and 53-54 under 35 U.S.C. § 102(e)

### The Rejection Under 35 U.S.C. § 103(a) (cited references)

Claims 36, 46, and 52 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over the '879 patent as applied to claims 29-35, 37-45, 47-51, and 53-54 above, and further in view of Berkower.

In response, Applicants response above under the 102 reference has eliminated the relevance of the '879 patent to the pending claims. Berkower does not teach, disclose or infer antibodies that bind SEQ ID NO:2.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 36, 46 and 52 under 35 U.S.C. § 103(a).

Appl. No. 09/990,046

Amend. dated March 21, 2005

Response to Office Action mailed on: December 20, 2004

**SUMMARY** 

Patent Docket P1405R1C1

Claims 29-54 are pending in the application. Claims 29, 39 and 49 have been amended

without prejudice to later prosecution.

If in the opinion of the Examiner, a telephone conference would expedite the

prosecution of the subject application, the Examiner is strongly encouraged to call the

undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter. In the unlikely event that

this document is separated from the transmittal letter or if fees are required, applicants petition

the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or

credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

GENENTECH, INC.

Date: March 21, 2005

Craig G.)Svoboda

Reg. No. 39,044

Telephone No. (650) 225-1489

170860

## Appendix

Apr-04-2003 11:40

Fram-USPTO BPA!

T-587 P.002/004 F-011

The opinion is support of the decision being entered today is not binding precedent of the Board.

Paper 13

Filed by:

Trial Section Merits Panel Box Interference Washington, D.C. 20231 Tel: 703-308-9797 Fax: 703-305-0942

Filed 4 April 2003

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

DAVID A. BUMCROT,

Junior Party (Patent No. 6,309,879),

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FREDERIC DE SAUVAGE and DAVID A. CARPENTER, PAT, & T.M. OFFICE BOARD OF PATENT APPEALS AND INTERFERENCES

Senior Party (Application No. 09/060,939).

Patent Interference 105,081 (NAGUMO)

Before SCHAFER, LANE, and NAGUMO, Administrative Patent Judges.

NAGUMO, Administrative Patent Judge.

JUDGMENT
(Pursuant to 37 CFR § 1.662(a))

#### Introduction

1. On April 2, 2003, junior party Bumcroft filed Paper 12, in which it conceded priority as to Count 1, the sole count in this interference, and acknowledged that the communication would be treated as a request for adverse judgment.

Apr-04-2009 11:40 From-USPTO BPA1

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T-587 P.009/004 F-011

Paper No. 13

Interference 105,081 Bumcrot v. De Sauvage

### Order

On consideration of the forgoing, it is:

ORDERED that judgment on priority as to Count 1 is awarded against junior party Bumcrot,

FURTHER ORDERED that Bumorot is not entitled to a patent containing claims 1-13 of Bumorot's 6,309,879 patent, which correspond to Count 1;

FURTHER ORDERED that copies of this decision be given appropriate paper numbers and be entered in the administrative record of Bumcrot's 6,309,879 patent and De Sauvage's 09/060,939 application.

STCHARD R. SCHAFER

Administrative Patent Juge

SALLY GARDNER LANE

Administrative Patent Judge

WARK NACITMO

Administrative/Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

INTERFERENCE TRIAL SECTION +7093050843

T-597 P.004/004 F-011

Paper No. 13

Interference 105,081 Bumcrot v. De Sauvage

cc (via Facsimile and first class mail):

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TRIAL DIVISION

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GGCGTCGTGG K GGTCGAGCTT H TAGCGGCGGG GAGTCTCTCG ACGGGGGCTC AATGTGTGGG E >-AGGATCCCCG GGGAATTCCG GCATGACTCG ATCGCCGCCC CTCAGAGAGC TGCCCCGAG ഗ D, D. (1) œ D, Q, ഗ SECULO DE SE TCCTAGGGGC CCCTTAAGGC CGTACTGAGC 201 TCGACTCTAG AGCTGAGATC

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COTOBACCOA GGGAAACGGA GGGAACTOOC GAAGGCCOTO GACGATOTOT TOOGTGTOOA COOGGTOOGG ATGCACCOOG COGGGACAGA GGCCCTGTCT 901 GGAGCTGGGT CCCTTTGCCT CCCTTGAGGG CTTCCGGGAG CTGCTAGACA AGGCACAGGT GGGCCAGGCC TACGTGGGGC 4 0 Ĺų s. 224

CACCCCGAC GGTACCGAAG AGGGTGTTTA 1001 GACCTCCACT GCCCACCTAG TGCCCCCAAC CATCACAGCA GGCAGGCTCC CAATGTGGCT CACGAGCTGA GTGGGGGCTG CCATGGCTTC ပ ပ CTGGAGGTGA CGGGTGGATC ACGGGGGTTG GTAGTGTCGT CCGTCCGAGG GTTACACCGA GTGCTCGACT H E × > × Q A P ഗ Z G K ഗ U L 257

1101 TCATGCACTG GCAGGAGAA TTGCTGCTGG GAGGCATGGC CAGAGACCCC CAAGGAGAG TGCTGAGGGGC AGAGGCCCTG CAGAGCACCT TCTTGCTGAT TCTCCGGGAC A L AGTACGTGAC CGTCCTCCTT AACGACGACC CTCCGTACCG GTCTCTGGGG GTTCCTCTG ACGACTCCCG A H <u>ი</u> 万 万 G M 1. 1. G **(1)** [1] Σ 291

GAGTCCCCGC CAGCTGTACG AGCATTTCCG GGGTGACTAT CAGACACATG ACATTGGCTG GAGTGAGGAG CAGGCCAGCA CAGTGCTACA AGCCTGGCAG GICCGGICGI GICACGAIGI ICGGACCGIC 3 n O 4 0 CICAGGGGG GICGACAIGC ICGIAAAGGC CCCACIGAIA GICIGIGIAC IGIAACCGAC CICACICCIC ធ ťΩ ഗ ვ დ O H L O χ Ω ပ H F K О .. .. ..

1301 CGGCGCTTTG TECACCTGGC CCAGGAGGCC CTGCCTGAGA ACGCTTCCCA GCAGATCCAT GCCTTCTCCT CCACCACCCT GGATGACATC CTGCATGCGT GACGTACGCA LHA GCCGCGAAAC ACGTCGACCG GGTCCTCCGG GACGGACTCT TGCGAAGGGT CGTCTAGGTA CGGAAGAGGA GGTGGTGGGA CCTACTGTAG E. ۲ A F н A S ы ы r u E E Ø r. 0 357 TOTOTERAGE CAGTGOTGCO CETETGETGE GAGGOTATOT GOTCATGOTG GCOTATGCOT GETGACOAT GCTGCGGTGG GACTGCGGCC AGTCCCAGGG CTGACGCGG TCAGGGTCCC დ დ AGAGACTICA GICACGACG GCACACCACC CICCGATAGA CGAGIACGAC CGGAIACGGA CACACIGGIA CGACGCCACC .\_ T > A Y A C Σ ı. G Y L R V V G A A ഗ 1401 391 1501 PICCGIGGGC CPIGCCGGGG PACTGCTGGT GGCCCTGGCG GTGGCCTCAG GCCTTGGGCT CTGTGCCCTG CTCGGCATCA CCTTCAATGC TGCCACTACC GAACGECECE ATGACGACEA EEGGGACEGE CACEGGAGTE EGGAACEEGG GACAEGGGAE GAGEGGTAGT GGAAGTTAEG AEGGTGATGG H € e z L G I CA ្ន ပ S A > 'A L A ר רי > L A G AAGGCACCCG ഗ .> 1501 CAGGIGCIGC CITICITGGC TCTGGGAATC GGCGTGGATG ACGTATICCT GCTGGCGCAT GCCTTCACAG AGGCTCTGCC TGGCACCCCT CTCCAGGAGC grocacgaeg Gaargaaccg agaccettag cogcacctac tgcataagga cgaccgcgta cggaagtgte tccgagacgg accgtgggga gaggtcttcg A L P A F T E LAH > ⊓ 'J G V D t G ж .1 >

1701 GCATGGGCGA GTGTCTGCAG CGCACGGGCA CCAGTGTCGT ACTCACATCC ATCAACAACA TGGCCGCCTT CCTCATGGCT GCCCTCGTTC CCATCCCTGC CETACCEGET CACAGACGIC GCGIGCCCGI GGICACAGCA TGAGIGTAGG TAGITGITGI ACCGGCGGAA GGAGIACCGA CGGGAGCAAG GGIAGGGACA E, I N N N и Б Σ

ATTCAGATCC TGCCCCAGGA GCTGGGGGAC GGGACAGTAC GGATGCCGCC TCACCAACCG ACGTGGAAAC ATCGGCACTA CGAACAGAAG GGTCGGTAGG AGTCGGACCT TGCACCTTTG TAGCCGTGAT GCTTGTCTTC CCAGCCATCC TCAGCCTGGA Н Ø Q, נדי > N Ν ۲ TTCTCCCTAC AGGCGGCCAT AGTGGTTGGC > CGACGCTCGG AAGAGGGATG TCCGCCGGTA 1801 GCTGCGAGCC

CCCTGTCATG > CGACCCCCTG ტ TAAGTCTAGG ACGGGGTCCT α ρ. о н TGCTCAGGTG ACACGAGACG ACGAAGAGGT CAGGGACGAG ACGAGTCCAC A Q V 1901 CGCCACTGCC AGCGCCTTGA TGTGCTCTGC TGCTTCTCCA GTCCCTGCTC U D, (L, V L'C TCGCGGAACT ж 13 О GCGGTGACGG U 'n. 557

ATGGGTGACA CTTCGGTCGT CGGTCGTACA CCAGTGGTAG GACGGAGGGG TTCGGGTGGA ACTECCACAG TICAAGCCIT TACCCACIGI GAAGCCAGCA GCCAGCAIGI GGICACCAIC CIGCCICCCC AAGCCCACCI Ω, ם н E > > н ø S S ш U H ⊱ TGACGGTGTC AAGTTCGGAA Ø T > T A 2001 CAGTGGGCAT TGCCCACCTC GTCACCCGTA ACGGGTGGAG ۲, :1: 591

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CGGTAGCACG GCCCCGTTGC TGCTCCAGIC ACAIGCCAAG GCCAICGIGC TGTACGGTTC × CGGACGTTCA GGGACGGGAC ACGGGCGACC TTAGAACGGG TAAAGCGGGC GATAGTCAAA CGGGGCAACG ACGAGGTCAG 2201 GCCTGCAAGT CCCTGCCCTG TGCCCGCTGG AATCTTGCCC ATTTCGCCCG CTATCAGTTT Ο L >-K ш Z L A 3 æ O O 657

GACGGATGTG GTGCCTCGGG GCACCAAGGA CACGGAGCCC CGTGGTTCCT × Q, CTGCCTACAC > 0 E CTGGGCCTGA GCCTACGG AGCCACCTTG GTGCAAGACG GCCTGGCCCT TCGGTGGAAC CACGTTCTGC CGGACCGGGA r P 0 0 T L Ø ACCACGAGAA ACCACGAGAA GACCCGGACT CGGAGATGCC ... ... 2301 TGGTGCTCTT TGGTGCTCTT ٠., ч С ن.، د. 691

TTTGACTACG CCCATTCCCA ACGCGCCCTC AAACTGATGC GGGTAAGGGT TGCGCGGGAG œ Ħ Ω CGTACGGŁAG GACTCGCGGG TCGAGTCCAT GAAGAGGGAC ATGCTCCACC GGGACCACTG GGTCCCACCG 2401 GCATGCCTTC CTGAGCGCCC AGCTCAGGTA CTTCTCCCTG TACGAGGTGG CCCTGGTGAC CCAGGGTGGC د. ⊳ Y E V A <sub>۲</sub> K S :г.

AACTGGCTAC TTGACCGATG GATAATGGCG CTATTACCGC × × 2501 TITGAICIGC ACCAGGGCTI CAGIICCCIC AAGGCGGTGC IGCCCCCACC GGCCACCCAG GCACCCGGCA CCIGGCIGCA ↵ 3 œ AAACTAGACG TGGTCGCGAA GTCAAGGGAG TTCCGCCACG ACGGGGGTGG CCGGTGGGTC O K a a D, X A V ı, ഗ S α. U 'J

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FIG. 1C

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TITGCCCAGT TCCCCTTCCT GCTGCGTGGC CTCCAGAAGA CTGCAGACTT × Он 3 GAGTGTCCGG TTGAAGATGG GGGGTGGAGG വ Ω Ω >-ננו 4 0 ഗ CCACTCGTCA CTGGGGGACC CAGACCGTCG GGGGGAGAAC CTTCGCATCC CGCCAGCTCA GCCCTTGGAG LA P L G Ω ഗ > ATGTACCCCG ACTGGCACAC .∝ .> ACGACACCAC 2801 857

CCCCTCTTG GAAGCGTAGG GCGGTCGAGT CGGGAACCTC AAACGGGTCA AGGGGAAGGA CGACGCACCG GAGGTCTTCT GACGTCTGAA CTGGGGTGCA CGCCTACCCC AGCGGCTCCC CCTTCCTCTT CTGGGAACAG æ × Ø œ ٠, H Ĺ Ω K H TGTGGAGGCC ATCGAGGGGG CCCGGCCAGC ATGCGCAGAG GCCGGCCAGG ы ы Д Æ p, r R z ſιλ TGCTGTGGTG 2901 891

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GCTGAGTGCC ATCCCCGTGG TGATCCTTGT CGACCAGGAC CGCTACTACT GTCACCTTGA GAAACCATAG TACCCAAAGG ACCCGTAGTT CGACTCACGG TAGGGGCACC ACTAGGAACA .\_1 > > ഗ J GCGATGATGA CAGTGGAACT CTTTGGTATC ATGGGTTTCC TGGGCATCAA ပ tr L ω Σ U U ĹŦ ធា > Σ Σ GCCTCATAGT GCTGGTCCTG : : CGGAGTATCA 3201 4000

3301 GOCCTCTGTA GGCATTGGCG TTGAGTTCAC AGTCCACGTG GGTCTGGGCT TCCTGACCAC CCAGGGCAGC CGGAACCTGC GGGCGGCCA TGCCCTTGAG GCCTTGGACG CCCGGCGGGT ACGGGAACTC ᆸ z z CCGTAACCGC AACTCAAGTG TCAGGTGCAC CGAGACCCGA AGGAGTGGGTG GGTCCCGTCG ഗ ပ ø Ę > X > ₽ CCGGAGACAT 1024

GTAACATTCC ATGAAGAAAC GCTGGTTCCC ACTTTGACTT CATTGTAAGG TACTTCTTTG ÇL, > TAGAGGTGTA ACGACCCAGA CGAGTACGAA CGACCAAGGG TGAAACTGAA Д ſι ഗ O A 3401 CACACATTTG CCCCCGTGAC CGATGGGGCC ATCTCCACAT TGCTGGGTCT GCTCATGCTT Z Z ر. ပ ب. S GTGTGTAAAC GGGGGACTG GCTACCCCGG ပ Ω €--1057

CCTGGGCCCG CCGCCAGAGG TGATACAGAT GCCGCGACTG TCACGAGTGC GAGGACCCGG AGGAGGTACC TGAGCACGAC GACGGACACG ACGACAGGTA GGACCCGGGC GGCGGTCTCC ACTATGTCTA ပ ᄓ 3501 CGGCGCTGAC AGTGCTCACG CTCCTGGGCC TCCTCCATGG ACTCGTGCTG CTGCCTGTGC TGCTGTCCAT P V L G X G L' L ι. <

3501 GTACAAGGAA AGCCCAGAGA TCCTGAGTCC ACCAGCTCCA CAGGGAGGCG GGCTTAGGTG GGGGGCATCC TCCTCCCTGC CCCAGAGCTT TGCCAGAGTG TOGGGTCTCT AGGACTCAGG TGGTCGAGGT GTCCCTCCGC CCGAATCCAC CCCCGTAGG AGGAGGGACG GGGTCTCGAA ACGGTCTCAC ഗ <u>ი</u> a A Ωı CATGTTCCTT

3701 ACTACCTCCA TGACCGTGGC CATCCACCCA CCCCCCTGC CTGGTGCCTA CATCCATCCA GCCCCTGATG AGCCCCCTTG GTCCCCTGCT GCCACTAGCT TGATGGAGGT ACTGGCACCG GTAGGTGGGT GGGGGGGACG GACCACGGAT GTAGGTAGGT CGGGGACTAC TCGGGGGAAC CAGGGGACGA CGGTGATCGA P P L ۷ ۸

3801 CTGGCAACCT CAGTTCCAGG GGACCAGGTC CAGCCACTGG GTGAAAGAGC AGCTGAAGCA CAGAGACCAT GTGTGGGGCG TGTGGGGTCA CTGGGAAGCA GACCGTTGGA GTCAAGGTCC CCTGGTCCAG GTCGGTGACC CACTTTCTCG TCGACTTCGT GTCTCTGGTA CACACCCCGC ACACCCCAGT GACCCTTCGT

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GACCCAGACC ACAATCTGCG TCCTGC GGACCTCCCG GGACGACGAC GACGTAGGGG AGAGGGCTGG GTCGACAGTA CCCGGAGGGA CTATAGCTTA 3901 CTGGGTCTGG TGTTAGACGC AGGACGCCCTGGAGGGC CCTGCTGCTG CTGCATCCCC TCTCCCGACC CAGCTGTCAT GGGCCTCCCT GATATCGAAT

4001 TCAATCGATA GAACCGAGGT GCAGTTGGAC AGTTAGCTAT CTTGGCTCCA CGTCAACCTG

- (SEQ 10 NO: 3) GCTGGGGTGCACGCCTACCNCAGCGGNTCCCCCTTCCTCTTCTGGGAACA \*\*\*\*\*\*\* \*\*\*\*\* \*\*\*\*\*\*\*\* CTGGGGCTGTCCAGTTACCCCAACGGCTACCCCTTCCTCTTCTGGGAGCA hpatched GTATCTGGGCCTGCGGCGCTGCTTCCTGCTGGCCGTCTGCATCCTGCTGG \* \*\*\*\* \*\* \* \*\*\* \* \*\*\*\* \* \* \*\* \*\* \* \* \* GTACATCGGCCTCCGCCACTGGCTGCTGCTGTTCATCAGCGTGGTGTTGG hpatched TGTGCACTTTCCTCGTCTGTGCTCTGCTGCTCCTNAACCCCTGGACGGCT CCTGCACATTCCTCGTGTGCGCTGTCTTCTTCTGAACCCCTGGACGGCC hpatched GGCCTNATAGTGCTGGTCCTGGCGATGATGACAGTGGAACTCTTTGGŢAT GGGATCATTGTGATGGTCCTGGCGCTGATGACGGTCGAGCTGTTCGGCAT hpatched CATGGGTTTNCTGGGCATCAAGCTGAGT GATGGGCCTCATCGGAATCAAGCTCAGT hpatched 

> TCTGGGCCTGCGGCGCTCTCCTGCTGCCGCCGTCTGCATCCTGCTGGTGT \* \*\* \* \*\* \*\* GCTGCTGCTGTTCATCAGCGTGGTGTTGGCC---TGCACATTCCTCGTGT hpatched GCACTTTCCTCGTCTGTGCTCTGCTGCT \*\* \*\* \*\* \*\* \* GCGCTGTCTTCCTTCTGAACCCCTGGAC hpatched 31.50

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                GCTGGGGTGCACGCCTACCCCAGCGGCTCCCCCTTCCTCTTCTGGGAACA
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                {\tt CTGGGGCTGTCCAGTTACCCCAACGGCTACCCCTTCCTCTGGGAGCA}
       hpatched
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                 GTATCTGGGCCTGCGGCGCTGCTTCCTGCTGGCCGTCTGCATCCTGCTGG
       1326258
                 GTACATCGGCCTCCGCCACTGGCTGCTGCTGTTCATCAGCGTGGTGTTGG
       hpatched
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                 TGTGCACTTTCCTCNTCTGTGCTCT
       1326258
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                CCTGCACATTCCTCGTGTGCGCTGT
       hpatched
                                3130
              3110
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                       110
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       1326258
       {\tt GCTGCTGCTGTTCATCAGCGTGTGTTGGCC---TGCACATTCCTCGTGT}
hpatched
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                 150
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       GCACTTTCCTCNTCTGTGCTCT
1326258
       ** ** ** ***
       GCGCTGTCTTCCTTCTGAACCC
hpatched
             3140
       3130
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GRRRRIGGLRRAAAPDRD. GGRR PGRPAG GGSGCIGA PODRGG ш ⋖ AGNA

⋖

PSYCDAAFALEOISKGKATGRKAPLWLRAKFORLLFKLGCYIOKNCGK PSYTPP...ARTAAPOILAGSLKAPLWLRAYFOGLLFSLGCGIORHCGK Œ a. (SEQ ID NO:4) PTCH (SEQ ID NO:2) PTCH2

101 FILV VIGLE TIPEGAFANGE KAANLETNVEELWVE VGGRVSRE LNYTROKIIGEE 58 VIFE GELLAFGALAMAIIETNLEOLWVE VGSRVSQE LHYTKEKILGEE

AMFNPOLMIOTPKEEGANVLTTEALLOHLOSALOASRVHVYMYNROWKLE AAYTSOMLIOTAROEGENILTPEALGLHLOAALTASKVOVSLYGKSWOLN PTCH2

H L C Y K S G E L I T E T G Y M D O I I E Y L Y P C L II I T P L D C F W E G A K L O S G T A Y L L G K I C Y K S G V P L I E N G M I E W M L E K L F P C V L L T P L D C F W E G A K L O G G S A Y L P G 158 PTCH2

 $\triangleleft$ KPPLRWTNFDPLEFLEELKKINYOVDSWEEMUNKAEVGHGYMDRPCLNP, RPDIOWTNLDPEOLLEELGPFA.SLEGFRELLDKAOVGOAYVGRPCLHPI 251 PTCH2

DPDCPATAPNKNSTKPLDMALVLNGGCHGLSRKYMHWQEELIVGGTVKNS DLHCPPSAPNHHSRQAPNVAHELSGGCHGFSHKFMHWQEELLLGGMARDP 257 301

 $\widehat{(\cdot)}$ 

TIGKTOVSTAHALOT MFOLMTPKOMYEHFKGYEYVSH-TINWNEDKAAAILEAW OGELL RAEALOSTELL MSPROLYEHFRO DYOTHOLGWSEE OASTVLOAW 351 307 PTCH2

ORTYVEVVHOSVAONSTOKVLSFTTTTLDDILKSFSDV3VIRVASGYLLM Orrevencealpenasooihaessttlddilhaesevsaaamveggyllm PTCH2

∢ ∢ SH TM3 VGLAGVLLVALSVAAGLGLOSUIG VGLAGVLLVALAYASGLGLOALLGI 0 G A V O တ တ LAYACLTMERWDGSK 450 406 PTCH2

T G Q N K R 1 P F E D R T G E C L K R T G A S V A A L P G . . T P L Q E R M G E C L Q R T G T S V V AHAFSET AHAFTEP ) D V F L L A TM4

O TOVIPFLALGMGVDD

S TOVIPFLALGMGVDD 456 PTCH2

TM6 SLOAAVVVVFNFAMVELITEPATLSMD SLOAATVVVGCTFVAVMLVFRATLSLD TMS LTSTNNVTAFFMAALTPTALRAF LTSTNNMAAFUMAALVPTPALRAF 550

တ တ > d  $\mathbf{r}$ SS չ-գ. a. YRREDRRLDIFCCFTSPCVSRVIOVEPOAYTOTHDNTRYSPPI RRRHCORLDVLCCFSSPCSAOVIOILPOELGOGT..... 554 PTCH2 PTCH2 PTCH

TLSC PLGS TVOLRITEYDPHTHVYYTTAEPRSEISVOPVTVTOD TVOAFTHCEASSOHVVITILPPOAHLVPPP....SO ITMQS ..LTA H Y A H 650 PTCH2 PTCH

പഗ LEPPOTKWTLSSFAEKHYAPFLLK KSLPCARWNLAHFARYOFAPLLLO O K A A O S s ⊢ ESTSSTROLLSOFSD: SPGGSTROLLGOEEE ൨ ഗ O ш 700

× c ட ப TM7 Karvvvvi filegvstygttrvaciolto Hara ivlvvergtkehaflsadi 748

K M W L H FYNMY IVTOKA . DYPNIOHLLYDL HRSFSNVKYWMLEENKOLPI LYEVAL<u>VTOGGFDY</u>AHSORALFDLHORFSSLKAVLPPPATOAPI SS ս. ս.

FIG. 3B

YFROWLOGLODAFDSDWETGKIMPNNYKNGSDDGVLAYKLLVOTGSRDKP YYRNWLOGIOAAFDODWASGRITRHSYRNGSEDGALAYKLLIOTGDAOEP 784

PTCH PTCH2

/ E A | E K V R T EWVHOKADYMPETRLRIPAAEPIEYAOFPFYLNGLRDTSDFVIEWLHDKYDOTYD 884 PTCH2

I CSNYTSLGLSSYPNGYPFLFWEOY I GLRHWLLLFTSVVLACTFLVCAV F A CAEAGOAGVHAYPSGSPFLFWEOYLGLRRCFLLAVOILLVGTFLVCALL 664 933 PTCH2 PTCH

GVE F GVE F TM9

LUNPWTAG HVMVLALMTVELFGMMGLHGHKLSAVPVVHTHVSVGH 1047

TM11

TVHVALAFLTA I GOKNARAVLALEHMEAPVLOGAVSTLLGVLMLAGSEFI
TVHVALGFLTTOGSRNIRAAHALEHTFAPVTOGANSTLLGVLMLAGSHFI 1033 1097

വഗ \_ ய 6 L N R L TM12 EGULHGEVLEPVEESFFGPYPEVSPANI GGULHGEVLEPVEES = F A V |L A 1 | L T 1 | L = F A A |L T V | L T | L |L և և 7 > --1083

യ പ 000 ш ш ∢ SPEPPPSVVRFAMPPGHTHSGSDSSDSEYSSOTTVSGUSEELRHYI PPAPOGGGLRWGASSSLPOS-FARVTTSMTVAIHPPPLPGAYIHPA 1197

FIG. 3C

PTCH 1247 AGG|PA|HQVIVEATENPVFAHSTVVHPESRHHPPSNPRQQPHLDSGSLPPG PTCH2 1182 PWS|PA|ATSSGNLSSRGPGPATG

PTCH 1297 ROGOOPRRDPPREGLWPPLYRPRRDAFEISTEGHSGPSNRARWGPRGARS

PTCH 1347 HNPRNPASTAMGSSVPGYCOPITTVTASASVTVAVHPPPVPGPGRNPRGG

PTCH 1397 LCPGYPETDHGLFEDPHVPFHVRCERRDSKVEVIELQDVECEERPRGSSS

PTCH 1447 N

FIG. 3D

Upper 😹

**→** 4.4 Kb

Lower

**⊸**β Actin

FIG. 4

S. P.

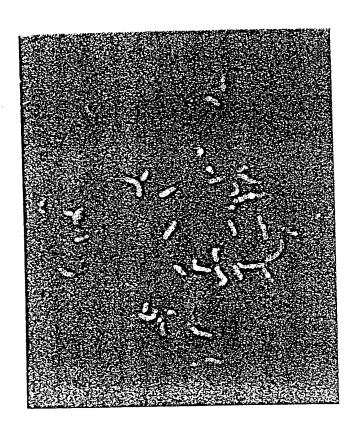
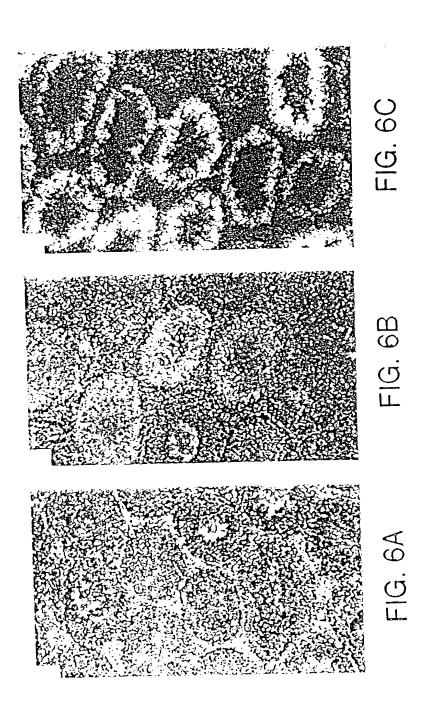
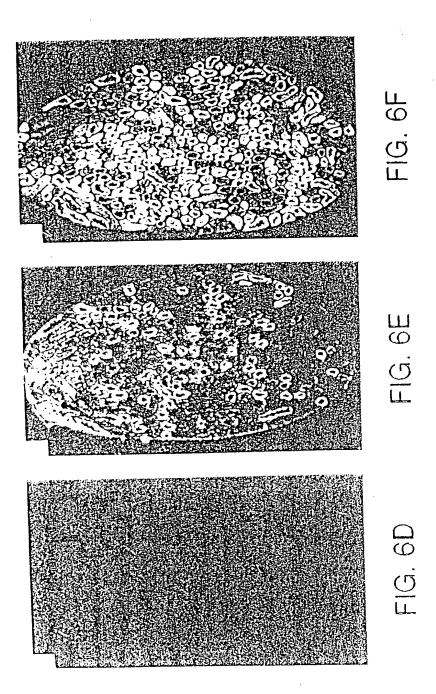
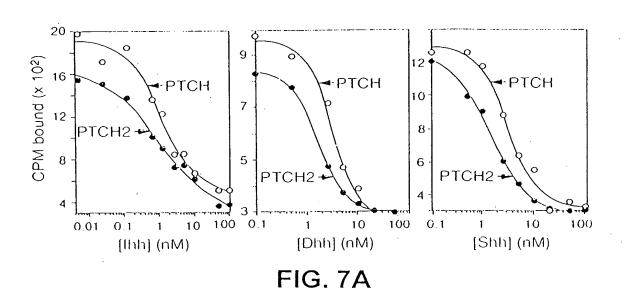


FIG. 5







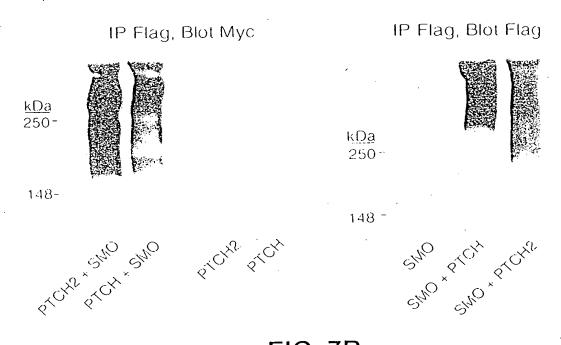


FIG. 7B

| h <i>Ptch-</i> 2              | 10<br>MTRSPPLRELPPS'<br>* ** *****                           | 20<br>(TPPARTAAPQ) | 30<br>[LAGSLKAPL        | 40<br>WLRAYFQGLL<br>***** | 50<br>FSLGCG<br>**** |
|-------------------------------|--|--------------------|-------------------------|---------------------------|----------------------|
| mPatched2                     | MVRPLSLGELPPS  | TPPARSSAPH         | ILAGSLQAPL<br>30        | WLRAYFQGLL<br>40          | FSLGCR<br>50         |
| hPtch-2                       | 60 IQRHCGKVLFLGL   | *****              | . * . * * * . * * *     | ****                      | ****                 |
| mPatched2                     | IQKHCGKVLFLGL<br>60  | VAFGALALGLR'<br>70 | VAVIETDLEQ<br>80        | LWVEVGSRVS<br>90          | QELHYT<br>100        |
| h <i>Ptch-</i> 2              | 110<br>KEKLGEEAAYTSQ<br>******                               | ****               | * . * * * * * * . *     | ****                      | ****                 |
| mPatched2                     | KEKLGEEAAYTSQ<br>110   | MLIQTAHQEGG<br>120 | NVLTPEALDI<br>130       | HLQAALTASK<br>140         | VQVSLY<br>150        |
| h <i>Ptch-</i> 2              | 160<br>GKSWDLNKICYKS<br>*****                                | *****              | . * * * * * * * * *     | ****                      | ****                 |
| mPatched2                     | GKSWDLNKICYKS<br>160   | GVPLIENGMIE<br>170 | RMIEKLFPCV<br>180       | /ILTPLDCFWE<br>190        | CGAKLQG<br>200       |
| h <i>Ptch-</i> 2<br>mPatched2 | 210<br>GSAYLPGRPDIQW<br>************************************ | ***** * * * * * *  | ****                    | ****                      | ****                 |
| h <i>Ptch-</i> 2<br>mPatched2 | 260 PCLHPDDLHCPPS ***.*** **** PCLDPDDPHCPPS                 | ****               | ***.*****<br>VVAQELSGGC | **********<br>HGFSHKFMHW  | ****                 |
| h <i>Ptch-</i> 2<br>mPatched2 | 310<br>GMARDPQGELLR<br>* *** ** ***<br>GTARDLQGQLLR<br>310   | ****               | *****                   | ****                      | ***                  |

FIG. 8A

| h <i>Ptch-</i> 2              | 360<br>VLQAWQRRFVQLA(<br>*******               | ****                         | ****                | *** ***                                 | ****                    |
|-------------------------------|--|------------------------------|---------------------|---|-------------------------|
| mPatched2                     | VLQAWQRRFVQLAG                                 | QEALPANASQQ<br>370           | HAFSSTTLD<br>380    | DILRAFSEVS<br>390                       | TTRVVG<br>400           |
| h <i>Ptch-</i> 2              | 410<br>GYLLMLAYACVTM:<br>*******               | ******                       | ****                | ****                                    | ****                    |
| mPatched2                     | GYLLMLAYACVTM<br>410                           | LRWDCAQSQG <i>F</i><br>420   | AVGLAGVLLVA<br>430  | ALAVASGLGLC<br>440                      | 450                     |
| h <i>Ptch-</i> 2<br>mPatched2 | 460 FNAATTQVLPFLA ******** FNAATTQVLPFLA 460   | *****                        | ***** * * .         | . * * * * * * * * * * * * * * * * * * * | ** * * *                |
| h <i>Ptch-</i> 2              | 510<br>SVVLTSINNMAAF<br>** *** *** **          | 520<br>T.MAALVPTPA)          | 530<br>LRAFSLOAAIV  | 540<br>VVGCTFVAVMI                      | 550<br>LVFPAIL<br>***** |
| mPatched2                     | SVALTSVNNMVAF                                  | FMAALVPIPA<br>520            | LRAFSLQAAI'<br>530  | VVGCNFAAVMI<br>540                      | LVFPAIL<br>550          |
| h <i>Ptch-</i> 2<br>mPatched2 | 560 SLDLRRRHCQRLE ****** *** SLDLRRRHRQRLE 560 | ****                         | ****                | *** . * * * * *                         | ***                     |
| h <i>Ptch-</i> 2              | 610<br>QAFTHCEASSQH <sup>V</sup>               | 620<br>VVTILPPQAHL<br>****** | 630<br>VPPPSDPLGS   | **. * * * * * * *                       | ***.**                  |
| mPatched2                     | OAFTHCEASSOH'                                  | VVTILPPQAHL<br>620           | LSPASDPLGS          | ELYSPGGSTR                              | DLLSQEE<br>650          |
| hPtch-2                       | 660<br>ETRQKAACKSLP<br>* ****                  | ** * ****                    | ******              | * * * . * * *                           | ****                    |
| mPatched2                     | GTGPQAACRPLL<br>660                            | CAHWTLAHFAF<br>670           | RYQFAPLLLQʻI<br>680 | TRAKALVLLFF<br>690                      | FGALLGLS<br>700         |

FIG. 8B

| h <i>Ptch-</i> 2<br>mPatched2 | 710 LYGATLVQDGLAL ******** LYGATLVQDGLAL 710 | ****                 | *****                 | *****                         | ****             |
|-------------------------------|--|----------------------|-----------------------|-------------------------------|------------------|
|                               | 760<br>HSQRALFDLHQRF                         | 770                  | 780                   | 790                           | 800<br>WOOD44    |
| h <i>Ptch-</i> 2              | HSQRALFDLHQRF                                | ******               | *******               | *** * * * * * * * *           | ****             |
| mPatched2                     | HSQRALFDLHQRF<br>760                         |                      |                       |                               |                  |
|                               | 810  | 820                  | 830                   | 840                           | 850              |
| h <i>Ptch</i> -2              | ASGRITRHSYRNG                                | *****                | ****                  | * * * * * * * * * *           | ***.**           |
| mPatched2                     | ASGRITCHSYRNO<br>810                         | SEDGALAYKL<br>820    | LIQTGNAQEP!<br>830    | LDFSQLTTRKI<br>840            | LVDKEGL<br>850   |
|                               | 860  | 870                  | 880                   | 890                           | 900              |
| h <i>Ptch</i> -2              | IPPELFYMGLTVV<br>*******                     | /VSSDPLGLAA.         | SQANFYPPPP)<br>****** | * * * * * * * * * *<br>FMPHDK | * * * * * * * *  |
| mPatched2                     | IPPELFYMGLTV                                 | WSSDPLGLAA           | SOANFYPPPP            | EWLHDKYDTT                    | GENLRIP          |
| mr accricaz                   | 860  | 870                  | 880                   | 890                           | 900              |
|                               | 910  | 920                  | 930                   | 940                           | 950              |
| h <i>Ptch</i> -2              | PAQPLEFAQFPFI<br>.*******                    | LRGLQKTADF           | VEAIEGARAA            | CAEAGQAGVH                    | AYPSGSP<br>***** |
| mPatched2                     | AAQPLEFAQFPFI                                | T.HGLOKTADE          | VEATEGARAA            | CTEAGOAGVH                    | AYPSGSP          |
| mPacchedz                     | 910  | 920                  | 930                   | 940                           | 950              |
|                               | 960  | 970                  | 980                   | 990                           | 1000             |
| h <i>Ptch-</i> 2              | FLFWEQYLGLRR(                                | CFLLAVCILLV<br>***** | CTFLVCALLL            | LNPWTAGLIV                    | LVLAMMT          |
| mPatched2                     | FLFWEQYLGLRR                                 | CFLLAVCILLV          | CTFLVCALLL            | LSPWTAGLIV                    | TMMAJVJ          |
|                               | 960  | 970                  | 980                   | 990                           | 1000             |
|                               | 1010   | 1020                 | 1030                  | 1040                          | 1050             |
| h <i>Ptch-</i> 2              | VELFGIMGFLGI<br>*******                      | KLSAIPVVILV          | /ASVGIGVEFT           | VHVALGFLTT                    | `QGSRNLR         |
| mPatched2                     | VELFGIMGFLGI                                 | KLSAIPVVILV          | /ASIGIGVEFT           | 'VHVALGFLT'S                  | HGSRNLR          |
|                               | 1010   | 1020                 | 1.030                 | 1040                          | 1050             |

FIG. 8C

|                  | 1060                  | 1070              | 1080        | 1090              | 1100          |
|------------------|-----------------------|-------------------|-------------|-------------------|---------------|
| h <i>Ptch-</i> 2 | AAHALEHTFAPVT         | DGAISTLLGL        | LMLAGSHFDF  | IVRYFFAALT        | VLTLLGL       |
| 14 .017 =        | ** *** ****           | ***.****          | *****       | * * * * * * * *   | * * * * * * * |
| mPatched2        | AASALEQTFAPVT         | DGAVSTLLGL        | LMLAGSNFDF  | IIRYFFVVLT        | VLTLLGL       |
|                  | 1060                  | 1070              | 1080        | 1090              | 1100          |
|                  | 1110                  | 1120              | 1130        | 1140              | 1150          |
| 10.10            | LHGLVLLPVLLSI         | LGPPPEVIQM        | YKESPEILSP  | PAPQGGGLRW        | GASSSLP       |
| hPtch-2          | **** *****            | *****.*.*.        | *****. *    | . * * * * * * * * | **            |
| mPatched2        | LHGLLLLPVLLSI         | LGPPPQVVQV        | YKESPQTLNS  | AAPQRGGLRW        | DRPPTLP       |
|                  | 1110                  | 1120              | 1130        | 1140              | 1150          |
| ,                | 1160                  | 1170              | 1180        | 1190              | 1200          |
| 10.10            | QSFARVTTSMTVA         | IHPPPLPGAY        | (IHPAPDEPPW | ISPAATSSGNL       | SSRGPGP       |
| h <i>Ptch-</i> 2 | ****                  | . * * * * * * * * | *.*****     |                   |               |
| mPatched2        | QSFARVTTSMTV <i>A</i> | LHPPPLPGAY        | VHPASEEPT   |                   |               |
|                  | 1160                  | 1170              | 1180        |                   |               |
| h <i>Ptch-</i> 2 | ATG                   |                   |             |                   |               |

FIG. 8D

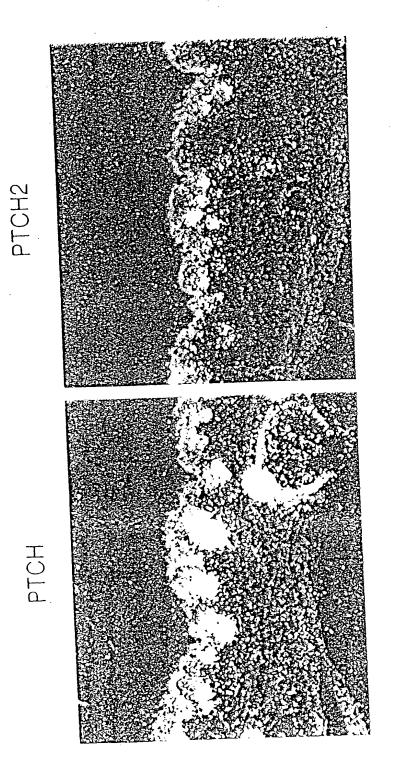


FIG. 9

msensus Sequence of human patched 2 cDNA clun

# d (8:0K GI DES)

1 CCCACGCGTC CGGGAGAAGC TGGGGGAGGA GGCTGCATAC ACCTCTCAGA TGCTGATACA GACCGCACGC CAGGAGGGAG AGAACATCCT CACACCGGAA respendict acquerater creecerece erecreeere remenaga ereregeem GGGTGCGCAG GCCCTCTTCG ACCCCTCCT CCGACGTATG 101 GCACTTGGCC TCCACCTCCA GGCAGCCCTC ACTGCCAGTA AAGTCCAAGT ATCACTCTAT GGGAAGTCCT GGGATTTGAA CAAAATCTGC TACAAGTCAG CGTGAACCGG AGGTGGAGGT CCGTCGGGAG TGACGGTCAT TTCAGGTTCA TAGTGAGATA CCCTTCAGGA CCCTAAACTT GTTTTAGACG

201 GAGTICCCCT TATIGAAAAT GGAATGATIG AGCGGATGAT TGAGAAGCTG TTTCCGTGCG TGATCCTCAC CCCCCTCGAC TGCTTCTGGG AGGGAGCCAA CTCAAGGGGA ATAACTITIA CCTTACTAAC TCGCCTACTA ACTCTTCGAC AAAGGCACGC ACTAGGAGTG GGGGGAGCTG ACGAAGACCC TCCCTCGGTT

ACTECAAGGG GGETECGGET ACCTGECGGET ECCAATGTGG ETEAEGAGET GAGTGGGGGE TGECATGGET TETECECACAA ATTEATGEAE TGGEAGGAGG TGAGGTTCCC CCGAGGCGGA TGGACGGCGA GGGTTACACC GAGTGCTCGA CTCACCCCCG ACGGTACCGA AGAGGGTGTT TAAGTACGTG ACCGTCCTCC 301

401 ANTECTICA GGGGGCATG GCCAGAGACC CCCAAGGAGA GCTGCTGAGG GCAGAGGCCC TGCAGAGCAC CTTCTTGCTG ATGAGTCCCC GCCAGCTGTA TTAACGACGA CCCTCCGTAC CGGTCTCTGG GGGTTCCTCT CGACGACTCC CGTCTCCGGG ACGTCTCGTG GAAGAACGAC TACTCAGGGG CGGTCGACAT

CGAGCATTIC CGGGGTGACT ATCAGACACA TGACATIGGC IGGAGTGAGG AGCAGGCCAG CACAGTGCTA CAAGCCTGGC AGCGGCGCTT IGTGCAGGTC GCTCGTAAAG GCCCCACTGA TAGICTGTGT ACTGTAACCG ACCTCACTCC TCGTCCGGTC GTGTCACGAT GTTCGGACCG TCGCCGCGAA ACACGTCCAG 501

601 GGTATGGACA AGGACAGGGG GGTGCCCTGA GGCCATTCCC TCCTCCTGCC CCCTCCTATC CACCCTGTTT CTCCAGCTGG CCCAGGAGGC CCTGCCTGAG CCATACCTGT TCCTGTCCCC CCACGGGACT CCGGTAAGGG AGGAGGACGG GGGAGGATAG GTGGGACAAA GAGGTCGACC GGGTCCTCCG GGACGGACTC

TTGCGAAGGG TCGTCTAGGT ACGSAAGAGG AGGTGGTGGG ACCTACTGTA GGACGTACGC AAGAGACTTC AGTCACGACG GGCACACCAC CCTCCGATAG AACGCTTCCC AGCAGATCCA TGCCTTCTCC TCCACCACCC TGGATGACAT CCTGCATGCG TTCTCTGAAG TCAGTGCTGC CCGTGTGGTG GGAGGCTATC 701

TECTCATEGT BESTETTECA CETEGERACET TECCECEREC CERCETECRA CERGTECECA CECTGGGGAG CECETGAGAE TECCETTTEC CECCACAGET ACGAGTACCA CCCAGAACGT GGACCGTGGA ACGGGGGTGG GGTGGAGGTT GGTCACGGGT GGGACCCCTC GGGGACTCTG ACGGGAAAGG GGGGTGTCGA 801

# FIG. 10A

TGCCCAGGAG TCGACGGGG AGGACGGG GAGGTCCACG ACGGGAAGAA CTGAGACCCT TAGCCGCACC TACTGCATAA GGACGACCGC GTACGGAAGT CAGAGGCTCT GCCTGGCACC CCTCTCCAGG TGGGGCCTTG TCCCCCAGGG CTCATCTGAG GCAGCTCAGC TTACTGGTTA AGAGCCTCTT GGTTCAAGTG AGETGCCCGC TCCTCTGCCC CTCCAGGTGC TGCCCTTCTT GACTCTGGGA ATCGGCGTGG ATGACGTATT CCTGCTGGCG 1101 ACGGGTCCTC 1201

AGACACGGGA CGAGCCGTAG TGGAAGTTAC GACGGTGATG GGTCCATGCG GTCCTGACGT CCCGTCTGAG TCACGGTCAG TGGTCCGAAG

GCTCGGCATC ACCTTCAATG CTGCCACTAC CCAGGTACGC CAGGACTGCA

GOCTTOGGC TCTGTGCCCT

1001

CCGGAACCCG

901 GOCCTATGCC TGTGTGACCA TGCTGCGGTG GGACTGCGCC CAGTCCCAGG GTTCCGTGGG CCTTGCCGGG GTACTGCTGG TGGCCCTGGC GGTGGCCTCA ceggataegg acacattest acgaegecae ectgaegegg steaggetee caaggeaeee ggaaeggeee catgaegaee aeegggaeeg eeaeeggaef CATGCCTTCA

GGGCAGACTC AGTGCCAGTC ACCAGGCTTC

GICTOCGAGA CGGACCGIGG GGAGAGGTCC ACCCCGGAAC AGGGGGTCCC GAGIAGACTC CGTCGAGTCG AAIGACCAAI ICTCGGAGAA CCAAGIICAC

ACCTIGGGCT GCTAATGAAC CTCGGTGCCT CTTGTCCCCA TGTGTAAACA GGGGAAATAA TAGTGCTGTG TCCTAAGGGT TATTGTTTGG ATCAGTGAAG TGGAACCCGA CGATTACTTG GAGCCACGGA GAACAGGGGT ACACATTTGT CCCCTTTATT ATCACGACAC AGGATTCCCA ATAACAAACC TAGTCACTTC 1301

ATTGAGITCA ACTIACGAAT CITGICGGGT AGTATGCATG TACCATGGGT TATITACGAT CGGTGACACA ATACTGACGG GGTGGAGACG TGGGGITCAA ACCCCAAGIT TAACTCAAGT IGAATGCTTA GAACAGCCCA TCATACGTAC ATGGTACCCA ATAAATGCTA GCCACTGTGT TATGACTGCC CCACCTCTGC 1401

GGACTCGGAG GGGAAGTGAG GTGAAACTGT GCCGGGGAGG GAACACTGGA CTCCCGTCCA GGGGTGAGAC AGGACCGTCC TCGCGTACCC GCTCACAGAC CACTITGACA CGGCCCCTCC CITGIGACCI GAGGGCAGGI CCCCACICIG ICCIGGCAGG AGCGCAIGGG CGAGIGICIG CCTGAGCCTC 1501

CAGCGCACGG GCACCAGTGT TGTACTCACA TCCATCAACA ACATGGCCGC C'TTCCTCATG GCTGCCCTCG TTCCCATCCC TGCGCTGCGA GCCTTCTCCC STCGCGTGCC CGTGGTCACA ACATGAGTGT AGGTAGTTGT TGTACCGGCG GAAGGAGTAC CGACGGGAGC AAGGGTAGGG ACGCGACGCT 1601

TACAGECTEG ACCTACEGEG GEGECACTEC CAGEGECTTG ATGTECTETS CTGETTETEC AGGTACTECE TGEGECECEAG ECCETTECTE CEGTGACECA TEGATECCEC CECEGTGACE GTCECEGAAC TACACGAGAC GACGAAGAGG TCCATGACGG ACGCGGGGTC GGGGAAGGAG GGCACTGGGT ATGTCGGACC 1701

CECCABECTE TECECTEACE AGEATTEAA GGEACAGACE TETEATECAE TETETACETE TTECAGTECE TGCTCTGCTC AGGTGATTEA GATECTGEEC 1801

1901 CAGGAGCTGG GGGACGGGAC AGTACCAGTG GGCATTGCCC ACCTCACTGC CACAGTTCAA GCCTTTACCC ACTGTGAAGC CAGCAGCCAG CATGTGGTCA STCCTCGACC CCCTGCCCTG TCATGGTCAC CCGTAACGGG TGGAGTGACG GTGTCAAGTT CGGAAATGGG TGACACTTCG GTCGTCGGTC GTACACCAGT

2001 CCATCTGCC TCCCCAAGCC CACCTGGTGC CCCCACCTTC TGACCCACTG GGCTCTGAGC TCTTCAGCCC TGGAGGGTCC ACACGGGACC TTCTAGGCCA GETAGGACGG AGGGITCGG GTGGACCACG GGGGTGGAAG ACTGGGTGAC CCGAGACTCG AGAAGTCGGG ACCTCCCAGG TGTGCCCTGG AAGATCCGGT

COTOCTOCTO TETTOCETOT TOCETOGGAO GITOAGGGAO GGGACACGGG CGACOTTAGA ACGGGTAAAG CGGGCGATAG TOAAACGGGG CAACGACGAG GGÀGGAGGAG ACAAGGCAGA AGGCAGCCTG CAAGTCCTTG CCCTGTGCCC GCTGGAATCT TGCCCATTTC GCCCGCTATC AGTTTGCCCC GTTGCTGCTC 2101

GTCAGTGTAC GSTICCGGTA GCACGACCAC GAGAACCAC GAGAAGACCC GGACTCGGAG AIGCCTCGGI GGAACCACGI ICTGCCGGAC CGGGACTGCC 2201 CAGTCACATG CCAMGGCCAT CGTGCTGGTG CTCTTTGGTG CTCTTCTGGG CCTGAGCCTC TACGGAGCCA CCTTGGTGCA AGACGGCCTG

TACACCACGG AGCCCCGTGG TTCCTCGTAC GGAAGGACTC GCGGGTCGAG TCCATGAAGA GGGACATGCT CCACCGGGAC CACTGGGTCC CACCGAAACT AIGTGGIGCC TCGGGGCCACC AAGGAGCATG CCTTCCTGAG CGCCCAGCTC AGGTACTTCT CCCTGTACGA GGTGGCCCTG GTGACCCAGG GTGGCTTTGA 2301

CTACGCCCAC TCCCAACGCG CCCTCTTTGA TCTGCACCAG CGCTTCAGTT CCCTCAAGGC GGTGCTGCCC CCACGGCCA CCCAGGCACC CCGCACCTGG GATECSEGTE AGGETTGCGC GGAGAAACT AGACGTGGTC GCGAAGTCAA GGGAGTTCCG CCACGACGGG GGTGGCCGGT GGGTCCGTGG GGCGTGGACC 2401

GACGTGATAA TGGCGTTGAC CGATGTCCCT TAGGTCCGAC GGAAACTGGT CCTGACCCGA AGACCCGCGT AGTGGGCGGT GAGCATGGCG TTACCGAGAC 2501 CTGCACTATT ACCGCAACTG GCTACAGGGA ATCCAGGCTG CCTTTGACCA GGACTGGGCT TCTGGGCGCA TCACCCGCCA CTCGTACCGC AATGGCTCTG

TCCTACCCCG GGACCGGATG TICGACGAGT AGGICTGACC ICIGGGGTC CICGGAGACC TAAAGICGGI CCAACCCICT CCCGACCTCC CCAGGIGAIC 2601 AGGATGGGGC CCTGGCCTAC AAGCTGCTCA TCCAGACTGG AGACGCCCAG GAGCCTCTGG ATTTCAGCCA GGTTGGGAGA GGGCTGGAGG GGTCCACTAG

TACAGGGGCT GCAGGCCTCC TGGGCCCAGG CCTTCAGCCC TCTCTGCCTC TGCAGCTGAC CACAAGGAAG CTGGTGGACA GAGAGGGACT GATTCCACCC ATGTCCCCGA CGTCCGGAGG ACCCGGGTCC GGAAGTCGGG AGAGACGGAG ACGTCGACTG GTGTTCCTTC GACCACCTGT CTCTCCTGA CTAAGGTGGG 2701

CTCGAGAAGA TGTACCCCGA CTGGCACACC CACTCGTCAC TGGGGGACCC AGACCGTCGG AGTGTCCGGT TGAAGATGGG GGGTGGAGGA CTTACCGACG 2801 GAGCTCTTCT ACATGGGGCT GACCGTGTG GTGAGCAGTG ACCCCCTGGG TCTGGCAGCC TCACAGGCCA ACTTCTACCC CCCACCTCCT GAATGGCTGC

2901 ACGACAAATA CGACACCACG GGGGAGAACC TTCGCAGTGA GTCTTGGGGG GAGCTCGGCA AGAGCCTCAG CCTCGCCCAC ACAAGCCCTG AGCCTGAGGC rgcretttat ectstsstsc ccctcttss aascstcact casaacccc ctcsasccst tctcssastc ssascsssts tsttcsssac tcssactccs

3001 CCIGCCCACT CIGCCCCGIG CICACCGCCC IGICCCTCIC CCICTICICC CTCCCCTCC CCTCCACAGI CCCGCCAGCI CAGCCCTIGG AGITIGCCCA GGACGGETGA GACGGGGCAC GAGTGGCGGG ACAGGGAGAG GGAGAAGAGG GAAGGGGAGG GGAGGTGTCA GGGCGGTCGA GTCGGGAACC TCAAACGGGT

## FIG. 10C

GACTGCAGAC TTTGTGGAGG CCATCGAGGG GGCCCGGGCA GCATGCGCAG AGGCCGGCCA GGCTGGGGTG CCGACCCCAC CAAGGGGAAG GACGACGCAC CGGAGGTCTT CTGACGTCTG AAACACCTCC GGTAGCTCCC CCGGGCCCGT CGTACGCGTC TCCGGCCGGT 3101 GITCCCCITC CIGCIGCGIG GCCTCCAGAA

GTGCGGATGG GGTCGCCGAG GGGGAAGGAG AAGACCCTTG TCATAGACCC GGACGCCGCG ACGAAGGACG ACCGGCAGAC GTAGGACGAC CACACGTGAA CATCCTGCTG TGGCCGTCTG CACGCCTACC CCAGCGGCTC CCCCTTCCTC TTCTGGGAAC AGTATCTGGG CCTGCGGCGC TGCTTCCTGC 3201

recreating recreteding erecreaace ecregaeges resecteara stgastectr scaggaging ggacagagae acceeaect recerseeca AGGAGCAGAC ACGAGACGAC GAGGAGTTGG GGACCTGCCG ACCGGAGTAT CACTCACGAA CGTCCTCACC CCTGTCTCTG TGGGGTGGGA AGGGACGGGT 3301

CGGACAGTAG GGAGGACGGT CCTCGGGAGA CACTCGGGAC AGAGGGAGTC CACGACCAGG ACCGCTACTA CTGTCACCTT GAGAAACCAT AGTACCCAAA GGAGCCCTCT GTGAGCCCTG TCTCCCTCAG GTGCTGGTCC TGGCGATGAT GACAGTGGAA CTCTTTGGTA TCATGGGTTT CCTCCTGCCA GCCTGTCATC 3401

CCTGGGCAIC AAGCTGAGTG CCATCCCCGT GGTGATCCTT GTGGCCTCTG TAGGCATTGG CGTTGAGTTC ACAGTCCACG TGGCTCTGGT GAGCACGGGC SGACCCGTAG TTCGACTCAC GGTAGGGGCA CCACTAGGAA CACCGGAGAC ATCCGTAACC GCAACTCAAG TGTCAGGTGC ACCGAGACCA CTCGTGCCCG 3501

ACCCCGGGGA GGGACCAATC AGCTGATTCA GTATTCAACA CATATTGTTC AAGCCCCTAC TATGTGCTAG GTACTATTTA AGAATTTGGG CTGGGTGGAC CCTGGTTAG TCGACTAAGT CATAAGTTGT GTATAACAAG TTCGGGGATG ATACACGATC CATGATAAAT TCTTAAACCC GACCCACCTG TGGGGCCCCT 3601

GIGGIGGCIC ATTCCIGIAA TCCCAGCACT TIGGGAGGCC GAGGCGGGIG GATCACCTGA GGICGGGAGI TCGAAACCAG CCIGGCCAAC AIGGIGAAAC CACCACCGAG TAAGGACATT AGGGTCGTGA AACCCTCCGG CTCCGCCCAC CTAGTGGACT CCAGCCCTCA AGCTTTGGTC GGACCGGTTG TACCACTTTG 3701

GGACAGAAAT GATTITTATG TITITTAATC GGTCCGCACC ACCGTGTACG GTCATCAGGG TCGATGAAAC CTCCGACTCC GTCTTAACGA ACTTGGACCC 3801 CCTGTCTTTA CTARARATAC AAAAATTAG CCAGGCGTGG TGGCACATGC CAGTAGTCCC AGCTACTTTG GAGGCTGAGG CAGAATTGCT TGAACCTGGG

AGGCGAAGGT TGCAGTGAGC TGAGATCGTG CCATTGCACT CCAGCCTGGG CAACAAGAGT GCAACTCTCC GTCTCAAAAA AAAAAAAA AAGGGCGGCC PCGGCTTCCA ACGTCACTCG ACTCTAGCAC GGTAACGTGA GGTCGGACCC GTTGTTCTCA CGTTGAGAGG CAGAGTTTT TTTTTTTTT 3901

4001 GCGA

**₹** 

-1G. 10D

TTCGGGATG ACTCGATGGC GGCCCCTCAG AGAGCTGCCC CCGAGTTACA CACCCCCAGC TCGAACCGCA GCACCCCAGA TCCTAGCTGG GAGCCTGAAG AAGGCCGTAC TGAGCTAGCG GCGGGAGTC TCTCGACGGG GGCTCAATGT GTGGGGTCG AGCTTGGCGT CGTGGGGGTCT AGGATCGACC CTCGGACTTC

CGAGGTGAGA CCGAAGCACG AATGAAGGTC CCGGACGAGA AGAGAGACCC TACGCCCTAG GTCTCTGTAA CACCGTTTCA CGAGAAAGAC CCTGACAACC GCTCTTTCTG GGACTGTTGG GTGGCAAAGT 101 GETECACTET GECTTEGIGE TIACTICEAG GECETGETET TETETEGGG ATGEGGGATE CAGAGACATT

CCTGGCATTA GGTCTCCGCA TGGCCATTAT TGAGACAAAC TTGGAACAGC TCTGGGTAGA AGTGGGCAGC CGGGTGAGCC AGGAGCTGCA GGAAACCCCG GGACCGIAAT CCAGAGGCGT ACCGGTAATA ACTCTGTTTG AACCTTGTCG AGACCCATCT TCACCCGTCG GCCCACTCGG TCCTCGACGT CCTTTGGGGGC 201

TTACACCAAG GAGAAGCTGG GGGAGGAGGC TGCATACACC TCTCAGATGC TGATACAGAC CGCACGCCAG GAGGGAGAGA ACATCCTCAC ACCCGAAGCA CTCCCTCTCT TGTAGGAGTG TGGGCTTCGT AATGTGGTTC CTCTTCGACC CCCTCCTCCG ACGTATGTGG AGAGTCTACG ACTATGTCTG GCGTGCGGTC 301

CTTGGCCTCC ACCTCCAGGC AGCCCTCACT GCCAGTAAG TCCAAGTATC ACTCTATGGG AAGTCCTGGG ATTTGAACAA AATCTGCTAC AAGTCAGGAG GAACCGGAGG TGGAGGTCCG TCGGGAGTGA CGGTCATTTC AGGTTCATAG TGAGATACCC TTCAGGACCC TAAACTTGTT TTAGACGATG TTCAGTCCTC 401

AAGGGGAATA ACTITIACCI TACTAACTCA CCTACTAACT CTICGACAAA GGCACGCACT AGGAGTGGGG GGAGCTGACG AAGACCCTCC CTCGGIITGA TICCCCTIAT TGAAAATGGA ATGATTGAGT GGATGATTGA GAAGCTGTTT CCGTGCGTGA TCCTCACCCC CCTCGACTGC TTCTGGGAGG GAGCCAAACT 501

CCAAGGGGGC TCCGCCTACC TGCCCGGCCG CCCGGATATC CAGTGGACCA ACCTGGATCC AGAGCAGCTG CTGGAGGAGC TGGGTCCCTT TGCCTCCCTT GGTTCCCCCG AGGCGGATGG ACGGGCCGGC GGGCCTATAG GTCACCTGGT TGGACCTAGG TCTCGTCGAC GACCTCCTCG ACCCAGGGAA ACGGAGGAAA 601

701 GAGGGCTTCC GGGGCTGCT AGACAAGGCA CAGGTGGGCC AGGCCTACGT GGGGGGCCC TGTCTGCACC CTGATGACCT CCACTGCCCA CCTAGTGCCC CTCCCGAAGG CCCTCGACGA TCTGTTCCGT GTCCACCCGG TCCGGATGCA CCCCGCCGGG ACAGACGTGG GACTACTGGA GGTGACGGGT GGATCACGGG

801 CCAACCATCA CAGCAGGCAG GGTCCCAATG TGGCTCACGA GCTGAGTGGG GGCTGCCATG GCTTCTCCCA CAAATTCATG CACTGGCAGG AGGAATTGCT GETTGETAGT GICGICCGIC CGAGGGTTAC ACCGAGIGCI CGACICACCC CCGACGGTAC CGAAGAGGGI GITTAAGTAC GIGACCGICC ICCTTAACGA

GETEGGAGGE ATGGECAGAG ACCCCCAAGG AGAGCTGCTG AGGGCAGAGG CCCTGCAGAG CACCTTCTTG CTGATGAGTC CCCGCCAGCT GTACGAGCAT CGACCCTCCG TACCGGTCTC TGGGGGTTCC TCTCGACGAC TCCCGTCTCC GGGACGTCTC GTGGAAGAAC GACTACTCAG GGGCGGTCGA CATGCTCGTA 901

# FIG. 11A

AAGGCCCCAC TGATAGICIG IGTACIGIAA CCGACCICAC ICCICGICCG GICGIGICAC GAIGITCGGA CCGICGCCGC GAAACACGIC GACCGGGTCC GGCTGGAGTG AGGAGCAGGC CAGCACAGTG CTACAAGCCT GGCAGCGGCG CTTTGTGCAG CTGGCCCAGG 1001 TTCCGGGGTG ACTATCAGAC ACATGACATT

AGGCCCTGCC TGAGAACGCT TCCCAGCAGA TCCATGCCTT CTCCTCCACC ACCCTGGATA ACATCCTGCA TGCGTTCTCT GAAGTCAGTG CTGCCCGTGT TECGGGACGG ACTETTGEGA AGGGTEGTET AGGTAEGGAA,GAGGAGGTGG TGGGAECTAT TGTAGGAEGT AEGEAAGAGA ETTEAGTEAE GAEGGGEACA 1101

GGIGGGAGGC TAICTGCTCA IGCIGGCTA IGCCIGIGIG ACCAIGCTGC GGIGGGACTG CGCCCAGICÇ CAGGGITICCG IGGGCCTIGC CGGGGIACIG CCACCCTCCG ATAGACGAGT ACGACCGGAT ACGGACACAC TGGTÀCGACG CCACCCTGAC GCGGGTCAGG GTCCCAAGGC ACCCGGAACG GCCCCATGAC 1201

GACCACCGGG ACCGCCACCG GAGTCCGGAA CCCGAGACAC GGGACGAGCC GTAGTGGAAG TTACGACGGT GATGGGTCCA CGACGGGAAG AACCGAGACC CICAGGCCTT GGGCTCTGTG CCCTGCTCGG CATCACCTTC AATGCTGCCA CTACCCAGGT GCTGCCCTTC TTGGCTCTGG TGGCGGTGGC CTGGTGGCCC 1301

CACAGAGGCT CTGCCTGGCA CCCCTCTCCA GGAGCGCATG GGCGAGTGTC TGCAGCGCAC CITAGCCGCA CCIACIGCAI AAGGACGACC GCGTACGGAA GIGICICCGA GACGGACCGI GGGGAGAGGI CCICGCGIAC CCGCICACAG ACGICGCGIG GAATCGGCGT GGATGACGTA TTCCTGCTGG CGCATGCCTT 1401

CTTACAGCCA CCCGTGGTCA CAGCATGAGT GTAGGTAGTT GTTGTACCGG CGGAAGGAGT ACCGACGGGA GCAAGGGTAG GGACGCGACG CTCGGAAGAG GAATGTCGGT GGGCACCAGT GTCGTACTCA CATCCATCAA CAACATGGCC GCCTTCCTCA TGGCTGCCCT CGTTCCCATC CCTGCGCTGC GAGCCTTCTC 1501

TECTEAGEET GEACETAEGG EGGEGECACT GECAGEGEET, TGATGTGETE TGETGETTET CEAGTECETG CTCTGCTEAG GTGATTEAGA TECTGECECA AGGAGTOGGA CCTGGATGCC GCCGCGGTGA CGGTCGCGGA ACTACACGAG ACGACGAAGA GGTCAGGGAC GAGACGAGTC CACTAAGTCT AGGACGGGGT 1601

cetebacece etsecetste atssteacee staacsssts sastsaest steaasttes saatsssts acaettesst estesstest acaeeass TGTGGTCACC GACGGGACAG TACCAGTGGG CATTGCCCAC CTCACTGCCA CAGTTCAAGC CTTTACCCAC TGTGAAGCCA GCAGCCAGCA GGAGCTGGGG 1701

ATCCTGCCTC CCCAAGCCCA CCTGGTGCCC CCACCTTCTG ACCCACTGGG CTCTGAGCTC TTCAGCCCTG GAGGGTCCAC ACGGGACCTT CTAGGCCAGG TAGGACGGAG GGGTTCGGGT GGACCACGGG GGTGGAAGAC TGGGTGÁCCC GAGACTCGAG AAGTCGGGAC CTCCCAGGTG TGCCCTGGAA GATCCGGTCC 1801

1901 AGGAGGAGAC AAGGCAGAAG GCAGCCTGCA AGTCCCTGCC CTGTGCCCGC TGGAATCTTG CCCATTTCGC CCCGGAATTC CTGCAGCCCG GGGGATCCAC TICCGICITC CGICGGACGI ICAGGGACGG GACACGGGCG ACCITAGAAC GGGTAAAGCG GGGCCITAAG GACGICGGGC CCCTAGGIG

TAGTICTAGA GCGGCCGCCA CCGCGGTGGA GCTCCAGCTT TTGTTCCCTT TAGTGAGGGT TAATTGCGCG CTTGGGTATC TT ATCAAGATCT CGCCGGCGGT GGCGCCACCT CGAGGTCGAA AACAAGGGAA ATCACTCCCA ATTAACGCGC GAACCCATAG AA TAGTICTAGA GCGGCCGCCA CCGCGGTGGA GCTCCAGCTI TIGITCCCTT TAGTGAGGGT TAATTGCGCG CTTGGGTATC 2001

## FIG. 11B

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